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A New Approach to Clavalanine β-Lactam Antibiotic: Transformation of Chiral α-Furfuryl Amide into the δ-Hydroxyl-α-amino Lactones via Asymmetrical Dihydroxylation

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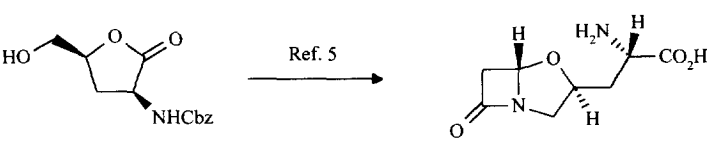
Abstract: Transformation of chiral α-furfuryl amide obtained from kinetic resolution into four δ-hydroxyl-α-amino lactones by utilizing the Sharpless ADH reaction as a key step was achieved.

The unusual amino acids, non-protein hydroxyl α-amino acids[1], isolated from the metabolisms of plants, bacteria, molds and lower marine animals[2], are very useful precursors in the synthesis of β-lactams[3]. Their syntheses have prompted a number of organic chemists to find efficient and convenient methods toward these natural products.

The (S, S)- δ-hydroxyl-α-amino lactone, (2S, 4S)-2-[(benzyloxycarbony) amino]-4-hydroxymethyl butyric acid γ-lactone (S, S)-**1** has been used as a precursor for synthesis a clavam antibiotic, clavalanine isolated from *Streptomyces clavuligerus*[4] in 1983. This β-lactam antibiotic is unique for being an antimetabolite of *O*-succinylhomoserine and intervention in methionine biosynthesis, whereas most of β-lactam antibiotics inhibit peptidoglycin biosynthesis[4c]. This precursor was synthesized by the Hoffmann-La Roche group from D-xylose in the total synthesis of clavalanine[5] (Scheme 1). Later, Williams and co-workers[6] have prepared (S, S)-**1** using an electrophilic glycine template obtained through resolution of a suitable racemic precursor. Ariza and co-workers[7] have synthesized **1** using D-ribonolactone as a chiral precursor. Schmidt and co-workers[8] prepared **1** from the optical 2, 3-*O*-isopropylideneglyceraldehyde.

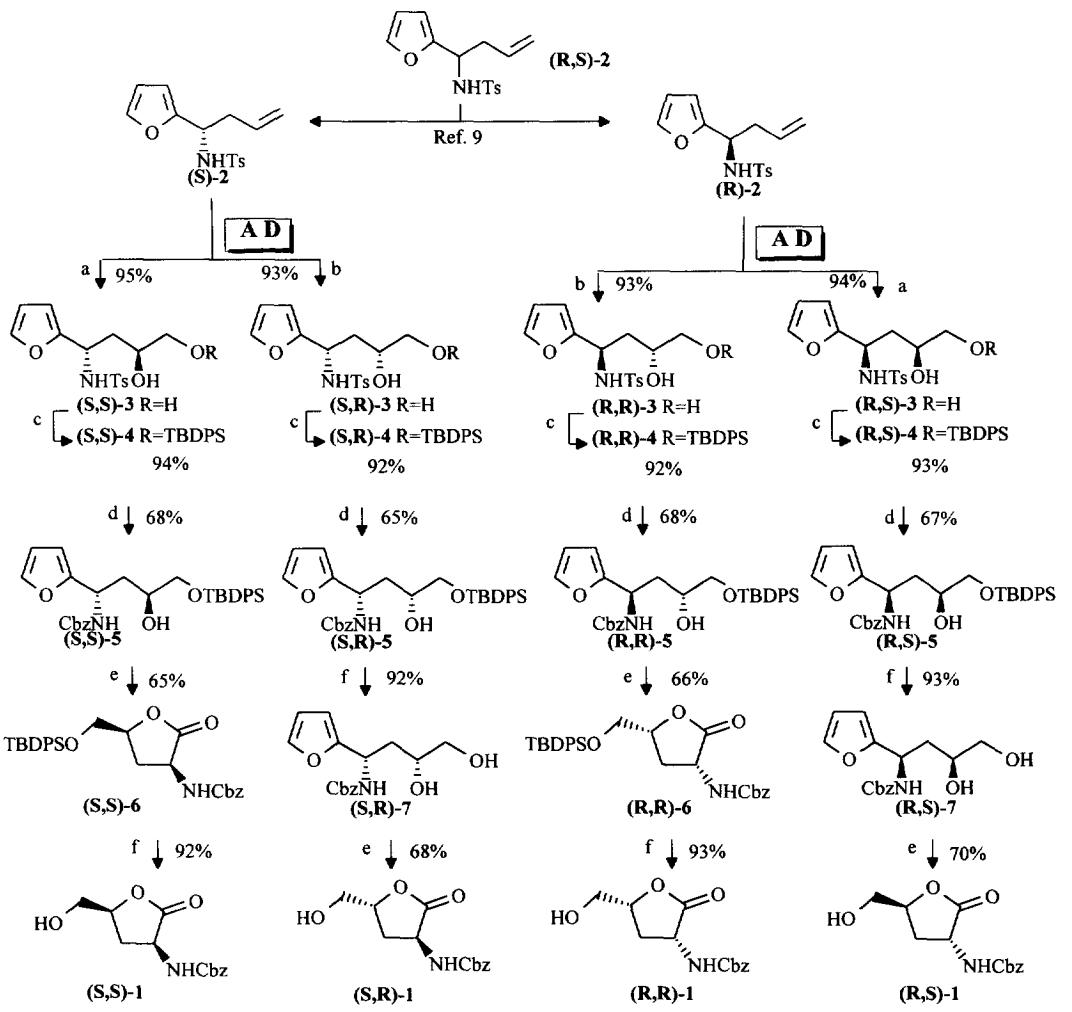
Scheme 1



(S, S)-**1** **Clavalanine**

In our previous work, an efficient method for kinetic resolution of α-furfuryl amide **2** by using the modified Sharpless asymmetric epoxidation was reported.[9] This reaction afforded two versatile chiral building blocks, α-furfurylamide and dihydropyridinone. Both of them are very suitable for synthesis of alkaloids[10] and α-amino acids[11]. Here, we report the syntheses of, in addition to (S, S)-**1**, another three stereoisomers (R, R)-**1**, (S, R)-**1** and (R, S)-**1** using one of chiral building blocks, (S)- α-furfuryl amide **2** and (R)- α-furfuryl amide **2**, respectively, from the kinetic resolution of the α-furfuryl amide (R, S)- **2**.

Scheme 2



Reagents and conditions: a. $K_2OsO_2(OH)_4$, K_2CO_3, $K_3Fe(CN)_6$, $(DHQ)_2$-PYR, *t*BuOH : H_2O = 1 : 1, r. t., 1d; b. $K_2OsO_2(OH)_4$, K_2CO_3, $K_3Fe(CN)_6$, $(DHQD)_2$-PYR, *t*BuOH : H_2O = 1 : 1, r. t., 1d; c. TBDPSCl, imidazole, THF, r.t.; d. i) Na/Naphthalene, DME, -78°C; ii) CbzCl, Na_2CO_3 (aqueous), 0°C; e. O_3, CH_2Cl_2 : MeOH = 12.5 : 1, $NaHCO_3$, -78°C; f. *n*-$Bu_4N^+F^-$, THF, r.t..

The syntheses of δ-hydroxyl-α-amino lactones (S, S)-**1**, (R, R)-**1**, (S, R)-**1** and (R, S)-**1** are depicted in Scheme 2. Kinetic resolution of α-furfuryl amide (R,S)-**2** with L-(+)-DIPT as a chiral ligand[9] yielded (S)-α-furfuryl amide **2** which on Sharpless asymmetric dihydroxylation (AD) using $(DHQ)_2$-PYR as the ligand[12] yielded 1,2-glycol (S, S)-**3**[13]. Selective protection of primary alcohol of (S, S)-**3** with *tert*-butyl diphenyl silyl chloride yielded (S, S)-**4**. Detosylation of (S, S)-**4** with sodium and naphthalene followed by protection of the amino group with benzyl chloroformate gave (S, S)-**5**, which on ozonization[14] in the presence of sodium hydrogen carbonate in CH_2Cl_2 : MeOH (12.5 : 1) afforded (S, S)-**6**[13]. Finally, deprotection of (S, S)-**6** with tetrabutylammonium fluoride yielded the known (S, S)-**1**[8,13]. Similarly, Sharpless asymmetric dihydroxylation of (S)-**2** using $(DHQD)_2$-PYR instead of $(DHQ)_2$-PYR as the ligand yielded 1,2-glycol (S, R)-**3**[13]. (S, R)-**4** was obtained by selective protection of primary alcohol of (S, R)-**3** with *tert*-butyl diphenyl silyl chloride. Detosylation of (S, R)-**4** with sodium and naphthalene followed by protection of amino group with benzyl chloroformate afforded (S, R)-**5**. When (S, R)-**5** was ozonized under the same condition as that of (S, S)-**5**, the protected δ-hydroxyl-α-amino lactone (S, R)-**6** could not be obtained as (S, S)-**6**. Since these two bulky protected groups are in *trans*-orientation during formation of five membered lactone ring, it is difficult to construct. Thus, (S, R)-**5** was deprotected first with tetrabutylammonium fluoride to yield (S, R)-**7** which on ozonization in the same condition as that of (S, R)-**5**[14] gave the known (S, R)- **1**[8,13]. Synthesis of the other two known isomers (R, R)-**1**[8,13] and (R, S)-**1**[8,13], utilizing (R)-**2** as a starting material, was similar to that of (S, S)-**1** and (S, R)-**1** depicted in Scheme 2.

Four δ-hydroxyl-α-amino lactones have been synthesized from the furfuryl amide (S)-**2** and (R)-**2**, respectively, which were obtained from the kinetic resolution of the α-furfuryl amide (R,S)-**2**. The overall yields of (S, S)-**1**, (S, R)-**1**, (R, R)-**1**, (R, S)-**1** are 36%, 35%, 36% and 38%, respectively, in 5 steps. These stereoisomers also could be used to probe the stereochemistry-biochemistry relationships for β-lactam antibiotic, Clavalanine.

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13.The data of some typical intermediate and target compounds are listed below: (S, S)-**3**. m.p.: 100.9 - 102.2°C; $[\alpha]_D^{20}$ -2.1° (c 3.8, EtOH); (R, R)-**3**. m.p. 100.6 - 102.3°C; $[\alpha]_D^{20}$ +2.3° (c 2.6, EtOH); ^{1}H-NMR (300MHz, $CDCl_3$)) of (S, S)-**3** and (R, R)-**3**: 7.57(*d*, 2H, *J*=7.56 Hz), 7.14(*d*, 2H, *J*=7.56 Hz), 7.05(*d*, 1H, *J*=1.9 Hz), 6.03(*dd*, 1H, *J*=1.9, 3.2 Hz), 5.73(*d*, 1H, *J*=3.2 Hz), 5.22(*d*, 1H, *J*=8.3 Hz), 4.58(*m*, 1H), 4.00(*m*, 1H), 3.54(*m*, 1H), 3.41(*m*, 1H), 2.31(*s*, 3H), 1.87(*m*, 2H). MS (*m/z*) of (S, S)-**3** and (R, R)-**3**: 326(M^++1), 170(M^+-Ts). HRMS (M^+-Ts) (for $C_8H_{13}NO_3$) of (S, S)-**3**: Calc. 170.0899; Found: 170.0858. (S, R)-**3**. m.p.: 98.5 - 100.0°C; $[\alpha]_D^{20}$ -2.4° (c 3.5, EtOH); (R, S)-**3**. m.p.: 98.7 - 100.3°C; $[\alpha]_D^{20}$ +2.8°(c 2.9, EtOH); ^{1}H-NMR (300MHz, $CDCl_3$) of (S, R)-**3** and (R, S)-**3**: 7.62(*d*, 2H, *J*=8.2 Hz), 7.20(*d*, 2H, *J*=8.2 Hz), 7.15(*d*, 1H, *J*=1.3 Hz), 6.12(*dd*, 1H, *J*=1.3, 3.2 Hz), 5.95(*d*, 1H, *J*=3.2 Hz), 5.35(*d*, 1H, *J*=8.3 Hz), 4.63(*m*, 1H), 3.64(*m*, 1H), 3.57(*m*, 1H), 3.43(*dd*, 1H, *J*=6.9, 9.6Hz), 2.38(*s*, 3H), 1.97(*m*, 1H) 1.89(*m*, 1H). MS (*m/z*) of (S, R)-**3** and (R, S)-**3**: 326(M^++1), 170(M^+-Ts). HRMS (M^+-Ts) (for $C_8H_{13}NO_3$) of (S, R)-**3**: Calc. 170.0817; Found: 170.0796. (S, S)-**6**. colorless oil, $[\alpha]_D^{20}$ +3.9°(c 2.0, EtOH). (R, R)-**6**. colorless oil, $[\alpha]_D^{20}$ -3.5°(c 2.1, EtOH). ^{1}H-NMR (300MHz, $CDCl_3$)) of (S, S)-**6** and (R, R)-**6**: 7.66-7.62(*m*, 4H), 7.48-7.33(*m*, 11H), 5.32(*d*, 1H, *J*=5.8 Hz), 5.14(*s*, 2H), 4.55(*br*, 1H), 4.50(*m*, 1H), 3.91(*dd*, 1H, *J*=3.54, 9.37Hz), 3.72(*dd*, 1H, *J*=3.71, 7.93Hz), 2.78(*m*, 1H), 2.10(*m*, 1H), 1.04(s, 9H). MS (*m/z*) of (S, S)-**6** and (R, R)-**6**: 446 (M^+ -^{t}Bu), 310(M^+-^{t}Bu-Cbz). HRMS (M^+-^{t}Bu) Calcd. for ($C_{21}H_{26}O_3NSi$) of (S, S)-**6**: 446.1423; Found: 446.1456. (S, S)-**1**. m.p. 116.3 - 117.3°C { Lit[8]. 118°C }; $[\alpha]_D^{20}$ +6.0° (c 1.6, MeOH) { Lit[8]. $[\alpha]_D^{20}$ +6.6° (c 0.24, MeOH) }; (R, R)-**1**. m.p.: 114.5 - 115.8°C { Lit[8]. 118°C }; $[\alpha]_D^{20}$ -6.3°(c 1.8, EtOH) { Lit[8]. $[\alpha]_D^{20}$ -7.1° (c 0.37, MeOH) }; ^{1}H-NMR (300MHz, $CDCl_3$) of (S, S)-**1** and (R, R)-**1**: 7.79(*d*, 1H, *J*=8.4 Hz), 7.40-7.30(*m*, 5H), 5.19(*m*, 1H), 5.05(*s*, 2H), 4.59(*dd*, 1H, *J*=2.0, 4.9 Hz), 4.51(*dd*, 1H, *J*=3.2, 4.9 Hz), 3.45-3.68(*m*, 2H), 2.21-2.42(*m*, 2H). (S, R)-**1**. m.p. 120.5 - 121.9°C { Lit[8]. 123°C }; $[\alpha]_D^{20}$ -46.0° (c 1.3, MeOH) { Lit[8]. $[\alpha]_D^{20}$ -50.1° (c 0.48, MeOH) }; (R, S)-**1**. m.p.: 118.3 - 120.1°C { Lit[8]. 121°C }; $[\alpha]_D^{20}$ +41.0° {c 0.35, EtOH) { Lit[8]. $[\alpha]_D^{20}$ +47.9° (c 0.52, MeOH) }; ^{1}H-NMR (300MHz, $CDCl_3$) of (S, R)-**1** and (R, S)-**1**: 7.75(*d*, 1H, J=8.4 Hz), 7.35(*m*, 5H), 5.05(*s*, 2H), 5.03(*m*, 1H), 4.41-4.49(*m*, 1H), 4.55(*m*, 1H), 3.46-3.63(*m*, 2H), 2.31-2.40(*m*, 1H), 1.94(*m*, 1H).

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